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Review Article

A review of acute febrile illness

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ABSTRACT

This review analyzes the epidemiology, clinical presentation, diagnosis, and treatment of major bacterial acute febrile illness (AFI). Existing studies on the AFI is focused the viral AFI agents, some bacterial and parasitic infections. Based on published literature only few studies have been able to identify major bacterial agents of AFI or show the importance of early diagnosis and treatment of AFI. In this review we focused on the most important bacterial AFI agents, which may help to understand how pathogenic the agents are and how crucial it is to diagnose them as early as possible.

1. Introduction

Fever is a common medical complaint with various causes, including infections, connective tissue diseases, malignancies, and several miscellaneous conditions. Acute febrile illness (AFI) is defined as a sudden rise in the body temperature above 38° Celsius (100.4 degrees Fahrenheit) for 2–14 days duration without any specific etiology.[1] AFI is a significant cause of morbidity and mortality in developing countries. AFI is India's most common cause of hospitalization. Acute undifferentiated febrile illness (AUFI) is a group of many unrelated medical conditions with the characteristics of persistent fever of unknown cause, despite basic investigations. Tropical infectious diseases can be caused by a variety of viruses, bacteria, or parasites. A patient may be suffering from several diseases at the same time, each with acute fever as a clinical symptom. This makes it difficult to determine the origin of the pathogen causing the disease.[2]

The common causes of AFI include enteric fever, brucellosis, leptospirosis, rickettsiosis, scrub typhus, melioidosis, Hantavirus infection, Japanese encephalitis, malaria, and dengue fever. Many individuals present with undifferentiated fever, categorized as AFI pending specific investigation for enteric fever, brucellosis, leptospirosis, rickettsiosis, scrub typhus, and melioidosis. AFI is caused by bacterial agents such as *Salmonella enterica serovar Typhi* (*S. Typhi*), *Salmonella enterica serovar paratyphi* A (*S. Paratyphi* A), *Burkholderia pseudomallei* (*B. pseudomallei*), Brucella species (Brucella spp.), Leptospira species (Leptospira spp.), Rickettsia species (Rickettsia spp.) and *Orientia tsutsugamushi (O. tsutsugamushi)* such as enteric fever, melioidosis, brucellosis, spotted fever, murine typhus, leptospirosis, and scrub typhus. These pathogens contribute to the global burden with a high incidence rate in South Asia, sub-Saharan Africa, East Asia, and the Pacific region.[3]

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2. Typhoid Fever

Typhoid and paratyphoid fever are both widespread, systemic infections caused by *S. Typhi* or *S. Paratyphi* A. Fever and rash are two significant typhoid symptoms. An effective way to confirm the diagnosis is to isolate the organism and test its sensitivity to antimicrobials through a blood culture. A result usually takes two to three days, and in the meantime, empirical antimicrobial treatment is necessary.[4] *Salmonella typhi: S. Typhi*, a gram-negative bacterium, is the cause of enteric fever and is the primary cause of morbidity and mortality worldwide. According to the World Health Organization (WHO), about 11 to 21 million people worldwide suffer from typhoid fever, with about 128,000 to 161,000 deaths annually.[5] *Salmonella paratyphi* A: *S. Paratyphi* A is the cause of paratyphoid fever in humans and is expected in Asia, Africa, the Middle East, and Central and South America. In humans, the routes of infection, spread, pathology, diagnosis, prevention, and treatment of paratyphoid fever are similar to those of typhoid fever. Contact with an affected person may also cause transmission. Paratyphoid fever can be life-threatening unless treated. Through the use of antibiotics, the infection is successfully treated.[6] Etiology of *S. Typhi* and *S. Paratyphi* A*: S. Typhi* and *S. Paratyphi* A are gram-negative, rod-shaped, flagellated, motile, and non-spore-forming bacterium in the family Enterobacteriaceae. In people with typhoid fever, the bacteria first travel through the intestinal tract and eventually enter the bloodstream. The resulting illness is often non-specific and clinically indistinguishable from other febrile illnesses.[7] Prevalence of typhoid fever: Globally, an estimated 11–20 million people get typhoid and 5 million cases of paratyphoid fever occur every year, and roughly 1, 28,000 to 1, 61,000 people die from it. Signs and symptoms of typhoid fever: Signs and symptoms of typhoid fever develop gradually, with the incubation period usually being 7 to 14 days. The illness begins slowly, with a gradual increase in fatigue and fever that rises daily from low grade to as high as 38°C to 40°C through the third to fourth day after illness. Fever is generally at its lowest in the morning and at its highest in the afternoon or in the evening. In severe cases, it can lead to serious complications and death.[8] Diagnostics tests for *S. Typhi* and *S. Paratyphi* A: Blood Culture – Laboratory diagnosis of typhoid fever requires isolation and identifying *S. Typhi*. The diagnosis of typhoid fever presently relies upon the isolation of the pathogen by blood culture. Typhoid fever is traditionally diagnosed using microbiological cultures collected from patients' blood, bone marrow, stool, and urine according to their illness. Blood cultures are considered the gold standard for diagnostic typhoid fever and are best done within a week of the onset of symptoms. Blood cultures required large samples for better results.[9] IgM – Detection of *S. Typhi*-specific IgM antibodies serves as a marker for recent infections and can be detected 2 to 3 days after the onset of symptoms. PCR-based amplification of *S. Typhi* genomic targets from typhoid fever patients' blood has now become available.[10] Treatment for typhoid fever: Specific antibacterial therapy for typhoid fever was unavailable until 1948 with the introduction of chloramphenicol, which was an anchor to the disease until the 1970s when resistance became common. Typhoid fever was treated with ampicillin, amoxicillin, and cotrimoxazole in the past, but current strains are resistant to these drugs. The current preferred drug is ciprofloxacin or ceftriaxone if the resistance is present. Taking antibiotics does not prevent typhoid fever; it only helps to treat it.[11] Prevention of typhoid fever: Safe drinking water, hygienic food, and proper medical care can help prevent and manage typhoid fever. Many developed countries have eliminated the risk through these measures, but unexpected failures can cause them. For this reason, some experts believe vaccines are the best way to control typhoid fever.[4] Vaccines for typhoid fever: Two typhoid vaccines, Ty21a (oral) and Vi polysaccharides, are widely used. Ty21a is a capsule-type live attenuated oral vaccine for people over five years old. Vi capsular polysaccharide vaccine (ViCPS) is an injectable vaccine based on the purified antigen for people aged over two years. More recently, a long-lasting immune typhoid conjugate vaccine (TCV) was pre-certified by WHO in December 2017 for use in children from the age of 6 months.[12]

3. Melioidosis

B. pseudomallei causes melioidosis, a fatal septicemic infection in humans that can at times become chronic and manifest as abscesses, chronic pneumonia mimicking tuberculosis, and fulminant septic shock with multiple abscesses in internal organs.[13] Etiology of *B. pseudomallei*: Humans and animals are thought to develop infections by inhaling contaminated dust, water droplets, ingesting contaminated water and soil-contaminated food or other contact with contaminated soil, especially skin scratches. Melioidosis is under-diagnosed and often mistreated as tuberculosis resulting in mortality.[14] Prevalence of Melioidosis**:** *B. pseudomallei*, saprophytic gram-negative bacteria, found in soil and water, widely distributed in tropical and subtropical countries. Melioidosis is an infectious disease endemic to South East Asia, North Australia, most of the Indian subcontinent, South China, Hong Kong, and Taiwan. India was predicted to be the most burdened with illness. Most people with melioidosis live in low- and middle-income countries. However, melioidosis is not one of the neglected tropical diseases listed by the WHO.[15] Signs and symptoms of Melioidosis**:** Melioidosis can spread from the skin through the blood to become a chronic degassing form that affects the heart, brain, liver, kidneys, joints, and eyes. The symptoms of melioidosis often stem from lung disease, where the

infection can form a cavity filled with pus.[16] Diagnostics tests for *B. pseudomallei*: Conventional diagnosis of B. pseudomallei by blood culture and serological identification using specific antiserum is routinely performed by a few hospitals and diagnostic laboratories in South and Southeast Asian countries where empirical use of antibiotics are widespread and available over the counter. In the case of melioidosis, the serological assays have not gained wide acceptance. Species-specific PCR assays provide a technically simple method for differentiating *B. pseudomallei* from near-neighbor species. Gene sequencing assays also used to differentiate the species specific analysis.[17] Treatment for Melioidosis: The treatment of melioidosis uses antibiotics and depends upon the disease's location. For patients with mild illness, the CDC recommends medication with antibiotics such as imipenem, meropenem, penicillin, doxycycline, amoxicillin-clavulanic acid, ceftazidime, ticarcillin-clavulanic acid, ceftriaxone, and aztreonam. Patients who are more seriously ill are given a combination of two drugs for 3 to 6 months. Prevention for melioidosis: People with open skin wounds and people with diabetes or chronic kidney disease are at increased risk of melioidosis and should avoid contact with soil and pooled water. Farmers should wear boots that can prevent infection from the feet and lower limbs.[14] Vaccines for Melioidosis: At present, there is no human vaccine against melioidosis. Because of these challenges, the development of melioidosis-fighting medical countermeasures has become a top priority in recent years.[18]

4. Brucellosis

Brucellosis is another important but neglected zoonotic disease with a worldwide distribution. It contributes significantly to economic losses for animal handlers. Transmission to humans occurs through contact with animals, animal tissue contaminated with the organisms, or through ingestion of contaminated products.[19] Etiology of Brucella: Brucellosis is caused by Brucella spp., composed of seven terrestrial species and at least two marine species. Terrestrial Brucella spp., include *B. abortus*, *B. melitensis*, *B. Suis*, *B. ovis*, *B. canis*, *B. neotomae*, and a newly discovered species, *B. microti*. Human brucellosis can be caused by any of the four major species: Brucellosis abortus, Brucellosis melitensis, Brucellosis suis, and Brucellosis Canis. In India, where cattle rearing are common, *B. abortus* and *B. melitensis* are known to cause AFI.[20] Prevalence of Brucellosis: Globally, 500,000 cases are reported every year, with 2.4 billion people at risk. All age groups are affected. The reported average prevalence rate of brucellosis in high risk population is found to be 8.5% in India.[21] Signs and symptoms of brucellosis: The symptoms of systemic brucellosis are often non-specific, including fever, fatigue, sweating, muscle pain, joint pain, back pain, and loss of appetite.[22] Diagnostics tests for Brucella: Worldwide, brucellosis is diagnosed by blood and bone marrow cultures or serological tests. The Brucella Serum agglutination test (SAT) is used despite its lower sensitivity and specificity.[23] PCR tests may be more sensitive and specific for diagnosing human brucellosis than blood cultures or traditional serological tests. Treatment for Brucellosis: As a standard supplement for adults, doxycycline for 45 days is combined with a daily dose of streptomycin IM, and for children, cotrimoxazole combined with gentamycin or rifampicin is recommended.[24] Prevention of brucellosis: Since most human infections are contracted through consuming contaminated milk, prevention involves verifying the presence of brucellosis in dairy animals. Vaccines for brucellosis: A live attenuated vaccine can be given to individuals at risk for occupational exposure. Vaccines have been developed for animals. An adequate vaccine is not available for human use.[25]

5. Rickettsiosis

Rickettsiosis/rickettsioses are a group of diseases commonly caused by the species of Rickettsia, a genus of obligate intracellular bacteria. The *Rickettsiaceae* family contains a diverse group of organisms that share common characteristics of intracellular proliferation and infection by hematogenous (blood-sucking) arthropod vectors, including ticks, lice, fleas, and mites. Invertebrates, including humans, infect vascular and reticuloendothelial cells. Rickettsiaceae is made up of three genera: Rickettsia, Orientia, and Ehrlichia. Rickettsial infections, if untreated, can have fatality rates as high as 30-35%, but when appropriately diagnosed, they are often easily treated.[26] Etiology of Rickettsia: Rickettsia is an obligate intracellular Gram-negative bacterium of the alphaproteobacterial class belonging to the order Rickettsiales. This group of organisms contributes to too many types of vector-borne diseases. There are two main groups of interest; the Spotted Fever Group and the Typhus Group.[27] Prevalence of Rickettsios: Generally, about 1-3% of the tick population carries R rickettsii, even in areas where most human cases are reported. Signs and symptoms of Rickettsios: The most common symptoms of the tick-borne rickettsial disease include fever, chills, nausea, vomiting, abdominal pain, encephalitis, hypotension, acute renal failure, respiratory distress, and headache (possibly severe).[28] Diagnostics tests for Rickettsios: The most common method for detecting and diagnosing Rickettsia is serology. The Culture methods are known to be more specific for detecting Rickettsial infection. Many rickettsial diseases go undiagnosed due to a lack of diagnostic tools. PCR methods for detection of Rickettsia Spp. in clinical samples include nested PCR and real-time PCR.[29] Treatment for Rickettsial group of diseases: Rickettsia is sensitive to tetracycline, chloramphenicol, and ciprofloxacin. Penicillin

Table 1: Recommended antibiotic treatment and dosage for AFI causing bacterial agents

Organism	Medication	Dosage		Duration
		Adult Dose	**Pediatric dosage**	
S. typhi and *S. paratyphi* A (Typhoid & Paratyphoid)	Ciprofloxacin	500 mg orally	IV: 400 mg IV every 12 hours. Oral: 500 mg orally every 12 hours	Every 12 hours for 10 days
	(If Resistance to ciprofloxacin) Azithromycin PO	1 g once daily	10 to 20 mg/kg once daily	7-14 days
	Ceftriaxone	2 g once daily or 2 times daily	50 to 100 mg/kg once daily	5-7 days
	Chloramphenicol IV	1 g 3 times daily	25 mg/kg 3 times daily	7-14 days
	Ampicillin IV	1 g every 6 to 8 hours	50 mg/kg every 6 to 8 hours	7-14 days
B. pseudomallei (Mellioidosis)	Ceftazidime (IV)	Ceftazidime 120mg/kg/day divided into 3 equal doses (maximum dose 2 gram/dose), diluted with 50ml normal saline solution IV	Every 8 hours for at least 10 days The dose will be adjusted according to the plasma creatinine level	minimum of 2 weeks (up to 8 weeks depending on extent of infection)
	Meropenem (IV)	Meropenem 1gm, diluted with 50ml normal saline solution IV	Every 8 hours for at least 10 days. The dose will be adjusted according to the creatinine clearance.	2 weeks
	Trimethoprim-sulfamethoxazole	160 mg/800 mg tablets; two tablets every 12 h	8 mg/40 mg per kg; maximum dose 320 mg/1600 mg every 12 h	taken every 12 hours (up to 3–6 months of oral antimicrobial therapy)
	Amoxicillin/clavulanic acid	500 mg orally	30 mg/kg to 15 mg/kg per day	Taken every 8 hours (up to 3–6 months of oral antimicrobial therapy)
Brucella spp	Doxycycline plus streptomycin 1 g	100 mg twice a day	5 mg/kg/day in two divided doses	45 days
	Doxycycline rifampicin at 15mg/kg/day	100 mg twice a day	5 mg/kg/day in two divided doses	45 days
Rickettsia spp	Doxycycline	100 mg orally twice daily for 7 days	2 .2 mg/kg per day in two equally divided doses	Five to Seven days
Leptospira spp (Leptospirosis)	**Mild disease:** Doxycycline	100 mg orally twice daily for 7 days	2 mg/kg per day in two equally divided doses	Seven days
	Severe disease: Penicillin	1.5 million units intravenously every six hours), doxycycline (100 mg IV twice daily), ceftriaxone (1 to 2 g IV once daily), or cefotaxime (1 g IV every six hours)	250,000 to 400,000 units/kg IV per day in four to six divided doses. doxycycline (4 mg/kg IV per day in two equally divided doses. ceftriaxone (80 to 100 mg/kg IV once daily, or cefotaxime (100 to 150 mg/kg IV per day in three to four equally divided doses	Seven days
O. tsutsugamushi (Scrub typhus)	Doxycycline	200 mg/day in two divided doses for individuals above 45 kg	4.5 mg/kg body weight/day in two divided doses for children below 45 kg	Seven days
	Azithromycin	500 mg in a single dose	10 mg/kg body weight	Five Days

and sulfonamides have no effect, but para-aminobenzoic acid has an inhibitory effect on Rickettsia. Sulfonamides promote the growth of Rickettsia and can exacerbate the condition when administered to patients. Prevention for Rickettsios: Rickettsial disease can be prevented by general measures such as controlling vectors and animal reservoirs.[30] Vaccines for Rickettsios: Killed and live vaccines have been prepared against epidemic typhus. The earliest of these phenolized intestinal contents of lice infected per rectum with prowazekii was developed. This was too complicated for mass production. Castaneda has developed a typhus vaccine by isolating R.prowazekii from the lungs of infected rats and inactivating the bacteria in formalin. Currently, no vaccines are available to prevent RMSF in either human or dogs.[31]

Table 2: The table indicates the gold standard techniques used for the detection of major AFI bacterial agents

Pathogen	Gold standard	
S. Typhi	Blood culture[32]	Song JH et al., 1993
S. Paratyphi A	Blood culture[32]	Song JH et al., 1993
B. pseudomallei	Blood culture[33]	Jesudason MV et al., 2005
Brucella species	IgM testing[34]	Welch RJ and Litwin CM., 2010
Leptospira species	IgM testing[35]	Tansuphasiri U et al., 2005
Rickettsia species	IgM testing[36]	Watthanaworawit W et al., 2013
O. tsutsugamushi	IgM testing[37]	Jones ML and Barnard RT., 2007

6. Leptospirosis

Leptospirosis is the most common disease in both wild and domestic mammals, and it is transmitted to humans through direct contact with an infected animal or indirectly through water or soil.[38] The genus Leptospira comprises both pathogenic and non-pathogenic species: *L. interrogans*, *L. borgpetersenii*, *L. weilii*, *L. noguchii*, *L. meyeri*, *L. fainei*, *L. alexanderi*, *L. santarosai*, *L. kirschneri*, *L. inadai*, *L. biflexa*, and *L. wolbachii*. Leptospirosis, long thought to be a sewage worker's disease and discovered post-flooding, is re-emerging as a potentially life-threatening infectious disease in urban India during the rainy season and immediately following due to poor cleanliness and drainage. Prevalence of Leptospirosis**:** Epidemics of leptospirosis are increasingly being reported in India, with most outbreaks being reported during the rainy season. Deodhar et al. reported 37.7% of Leptospiral infections in patients with AFI in Northern India.[39] Signs and symptoms of Leptospirosis: Leptospirosis symptoms and signs are highly variable and include no symptoms at all to nonspecific symptoms such as fever, chills, headaches, muscle aches and red eyes, vomiting, diarrhea, abdominal pain, cough, and sore throat. Diagnostics tests for Leptospira: The most common way to diagnose leptospirosis is through serological tests either the IgM ELISA or Microscopic Agglutination Test (MAT) which detects serovar-specific antibodies. Leptospira remain in the blood until they are cleared 4-7 days after the production of Leptospira-specific antibodies, primarily of the IgM class at first. PCR is very sensitive and specific test in the acute phase of illness, it picked up to 50% of cases which were negative by other serological tests.[40] Treatment for leptospirosis: Leptospires are susceptible to penicillin and tetracycline, but treatment must begin early during the illness to be effective. Penicillin is given intravenously, 1-2 million units for 6 hours over seven days in severe cases. A slight response of Jarisch-Herxheimar may occur in some. Oral doxycycline 200 mg once per week is adequate for prophylaxis.[41] Vaccines for leptospirosis**:** Several types of human leptospirosis vaccines have been developed, including inactivated whole-cell, outer-envelope, and recombinant vaccines.[42] Prevention for Leptospirosis: Leptospirosis can be prevented most effectively by avoiding potential sources of infection such as stagnant water, animal farm runoff, rodent control, and food that is not contaminated by animals.[41]

7. Scrub typhus

O. tsutsugamushi is an obligate intracellular pathogen belonging to the family Rickettsiaceae that causes the mite-borne human disease scrub typhus. If left untreated, the disease can worsen and cause multiple failures and fatalities. Scrub typhus is the most common re-emerging Rickettsial infection in India and many other Southeast Asian countries.[57] Etiology of scrub typhus: Mite larvae and chiggers transmit pathogenic gram-negative bacteria to humans through their bites, which serve as a vector. Prevalence of scrub typhus: Studies shows there is a wide range of prevalence for scrub typhus in different countries, ranging from 0–8% to 60%. Scrub typhus was reported in 25.3% of acute undifferentiated febrile illnesses (AUFI) studies, and 34.2% of community members had the disease.[58,59] Signs and symptoms of scrub typhus: The symptoms typically appear 7 to 14 days after a mite bite and may include headache, fever, myalgia, lymphadenopathy, maculopapular rash, and painless eschar at the site of the bite. Diagnostic tests for scrub typhus: Diagnosis of the scrub typhus remains an enigma in resource-limited settings like India. The confirmation of the diagnosis is usually by serological tests such as Weil Felix. The test is particular and cheap but less sensitive. Anti-O. tsutsugamushi IgG and IgM antibodies can be detected using commercially available ELISA kits in quick diagnostic tests. The drawbacks include poor availability and cost. PCR for detection of 47 kDa and 56 kDa protein gene of *O. tsutsugamushi* is reliable

Table 3: Set of primers used in nested PCR and Real-time PCR for the detection of bacterial AFI agents

Organism	Targeting gene	The Gene Encodes	Nested PCR Primers	Real-time PCR primers and probes
S. Typhi	FliC	Flagellin protein	OF: TATGCCGCTACATATGATGAG OR: TTAACGCAGTAAAGAGAG IF: ACTGCTAAAACCACTACT IR: TGGAGACTTCGGTCGCGTAG[44]	Fp-TGCTGATTTGACAGAGGCTAAA Rp- TCGCCTACCTTAACTGCTAAAC P- FAM –TGTTACCGGCACAGCATCTGTTGT-BHQ1[43]
S. Paratyphi A	SSPA	Hypothetical protein	OF: ACTGCTAAAACCACTACT OR: TTAACGCAGTAAAGACAG IF: AGATGGTACTGGCGTTGCTC IR: TGGAGACTTCGGTCGCGTAG[46]	R -GAAGACGACGAGGACGATGAC F-CCGCCGCTGCAATCA P-[FAM] ACGGGATGGTGGAGGT [MGB-NFQ][45]
B. pseudomallei	epaR	Type-III secretion apparatus protein	16S-23S spacer region IF: 5′ -CCTCCACCAATTGCGATGATCGTT-3′ IR: 5′-CAATCACAACCCGGATAGCTTCCAC-3′[47]	F: CCTGGGAGAGCGAGATGTT R: GCTGGATGAGAAGAAAGTCC TexasRed CCACGCACGGCGGAGATTCT-IAbRQ[48]
Brucella spp	Bcsp	Brucella cell surface protein	(orfA and orfB) OF: AACGTAACCATACATAGCGCATG OR: ACAGATGAGCAATGGAACCGGAT IF: GAATGGGTGCAATTTCTCGC IR: ATATCTTCCGGGGCGAGTTGGTA[50]	F: GCTCGGTTGCCAATATCAATGC R: GGGTAAAGCGTCGCCAGAAG 6FAM-AAATCTTCCACCTTGCCCTTGC CATCA-BHQ1[49]
Rickettsia spp	gltA	Citrate synthase encoding gene	OF: GGGGACCTGCTCACGGCGG OR: ATTGCAAAAAGTACAGTGAACC IF: GGCTAATGAAGCAGTGATAA IR: GCGACGGTATACCCATAGC[52]	F: CGGGGCACTCGGTATTGCTGTTT R: GCGAGCAGGAGTACCATTAGC FAM-GCAATAATTGGAATGAGATAACGG CTGC-TAMRA[51]
Leptospira spp	Lipl32	Leptospiral Outer membrane protein	OF: GGCGGCGCGTCTTAAACATG OR: TTCCCCCCATTGAGCAAGATT IF: TGCAAGTCAAGCGGAGTAGC IR: TTCTTAACTGCTGCCTCCCG[54]	F: AAGCATTACCGCTTGTGGTG, R: GAACTC CCATTTCAGCGA TT, P: FAM-AAAGCCAGGACAAGCGCCG-BHQ1[53]
O. tsutsugamushi	htrA	47-kDa periplasmic serine protease	OF: TCCTTTCGGTTTAAGAGGAACA OR: GCATTCAACTGCTTCAAGTACA IF: AACTGATTTTATTCAACTAATGCTGCT IR: TATGCCTGAGTAAGATACRTGAATRGAATT[56]	F: AACTGATTTTATTCAAACTAAT GCTGCT R: TATGCCTGAGTAAGATACRTGAATR GAATT P: FAM-TGGGTAGCTTTGGTGGACCGATGTTT AATCT - TAMRA[55]

and quantitative.[60] Treatment for Scrub typhus**:** Scrub typhus is treated with antibiotics such as doxycycline, tetracycline, chloramphenicol, rifampicin, azithromycin, or ciprofloxacin. A single dose of doxycycline has proved effective against scrub typhus. Doxycycline also works quickly on other strains of rickettsial disease.[61] Prevention for Scrub typhus: When traveling to regions where scrub typhus is common, people should avoid areas with lots of vegetation and brush where chiggers may be found. Vaccines for scrub typhus: According to the CDC reports, no vaccine is available to prevent scrubs typhus.

8. Available Treatment for Major Bacterial AFI Agents

The most effective antimicrobials against bacterial AFI agents are shown in Table 1. Recommended dosage for adults and children is given, as well as duration of treatment.(Table 1)

9. Gold Standard Tests for the Diagnosis of AFI Agents

Blood cultures are an essential test for detecting bacteriemia and determining bacteriological identity and its antibiotic sensitivity. Therefore, most physicians have a low threshold for obtaining blood cultures and initiating empirical antibiotics in patients with AFI. However, it is often difficult to estimate the likelihood of a bloodstream based on clinical judgment. Therefore, the yield of blood cultures is relatively low, and many false-positive contaminants can lead to unnecessary treatment. Attempts have been made to develop better diagnostic assays. However, most techniques are disappointing, and the attempt to replace bacterial cultures remains a commendable but elusive goal. Serological diagnosis is often relied on, although it suffers because of low sensitivity and specificity and cross-reactions between species. This complicates correct diagnosis and delays treatment, thus increasing morbidity and mortality. Because an effective treatment regimen is available for these infections, a clinically relevant specific identification of these pathogens using molecular techniques is warranted. Widely used gold standard techniques for diagnose the AFI are shown in Table 2.

The gold-standard diagnostic methods for detecting the seven AFI agents as described in previous research publications.

10. Molecular Assays for Detection of Seven Major Bacterial Agents Causing AFI

Table 3 shows the primers used in the nested PCR assay to detect the above-mentioned pathogens, as well as the primers and probes used in the real-time PCR assay.

11. Conclusion

AFI contributes to significant morbidity and mortality in children and adults worldwide. Over the last two decades, viral, bacterial, and parasitic infections have dramatically emerged. This includes novel pathogens and pathogens believed to be under control. AFI has several symptoms, including high-grade fever, headache, retro-orbital pain, hemorrhagic manifestations, skin rash, back pain, lymphadenopathy, and maculopapular rash. This phase of AFI usually lasts 2 to 14 days and is often characterized by generalized body pain, myalgia, arthralgia, exanthema, and headache. The non-specific symptoms of AFI are difficult to diagnose the pathogen and treatment. This review can help to understand the clinical presentations, diagnostic methods, available treatments and prevention for major bacterial agents causing the AFI.

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None.

13. Conflict of Interest

None.

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